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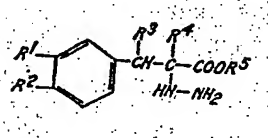
(54) PREPARATION OF L-α-HYDRAZINO-β-PHENYLPROPIONIC ACID COMPOUNDS

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with the preparation of *L* - α - hydrazino - β - phenylpropionic acid compounds.

The compounds prepared by the process according to the invention are valuable therapeutic agents and are covered by the general formula



in which each of R^1 and R^2 is a hydrogen atom or a hydroxy or C_{1-6} alkoxy, phenyloxy or benzyloxy group, each of R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl group and R^5 is a hydrogen atom, a metal atom or, in the case of a multivalent metal, an equivalent of the metal, or a C_{1-6} alkyl group. Racemates of α - hydrazino - α - substituted-β - (3,4 - dihydroxyphenyl) propionic acids and their esters are known, and they are known to be potent decarboxylase inhibitors in mammals. See Sletzinger et al "Journal of Medicinal Chemistry", volume 6, page 101 (1963) and Porter et al "Biochemical Pharmacology" Volume 11, page 1067 (November 1962). Such compounds have found use as medicaments.

The present invention is based on the discovery that the D-isomer of the racemate is inactive and to some degree even antagonistic to the action of the *L*-form, which is the active component and has been found to be a much more potent decarboxylase inhibitor than the previously known racemic compound. Thus, in some tests it appears that the *L*-form of the compound is the only active form and that the *D*-form is inactive. In other tests it appears that the *D*-form counteracts and detracts from the action of the *L*-form.

The inhibition of mammalian decarboxylase is an important part of the physiological action of many types of drugs. For example, it has recently been proposed to use *L*-dopa in the treatment of Parkinson's disease. However, *L*-dopa is utilized both in the brain and the peripheral parts of the body and it is desired

between water and chloroform. The organic layer is dried, the solvent is removed and the residue is crystallized from ethyl acetate and ether; the NMR spectrum of the residue indicated a 6:4 mixture of product and starting material. Chromatography on 30 g. of silica gel H (elution with chloroform and 3% methanol) yields 570 mg. (52%) of *L* - α - N¹ - acetylhydrazino - α - (3,4 - dimethoxybenzyl)propionitrile and 320 mg. of starting material. This represents a 56% direct yield or 80% based on unrecovered starting material.

By recrystallization from methanol a sample is obtained that melts at 121—123°:

Anal. calcd. for $C_{14}H_{19}N_3O_3$:
C, 60.63; H, 6.91; N, 15.15.
Found:
C, 60.82; H, 7.10; N, 15.21.

B. Hydrolysis of *L* - α - N¹ - acetylhydrazino - α - (3,4 - dimethoxybenzyl)-propionitrile to *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid

A solution of the product from the previous step (150 mg.) in 2.5 ml. of concentrated hydrochloric acid is heated in a sealed tube at 120° for 1-1/2 hours. After the usual workup procedure 50 mg. of hydrazino acid is obtained m.p. 208° dec.,

$[\alpha]_D^{25} = -17.3°$ (C=2, CH_3OH).

EXAMPLE 2

A. Preparation of *L* - α - N¹ - acetylhydrazino - α - (3,4 - dimethoxybenzyl)-propionic acid

To a slurry of 100 ml. of water, 200 ml. of ether 36 ml. of concentrated hydrochloric acid and 70.3 g. (0.25 mole) of *L* - N - acetyl - α - (3,4 - dimethoxybenzyl)alanine at 0—10° is added dropwise with vigorous stirring 18 g. (0.26 mole) of sodium nitrate in 36 ml. of water. The temperature is maintained at 0—10°C during addition and during one hour of stirring. The ethereal layer is separated, the aqueous layer is extracted with 100 ml. portions of ether, the combined ethereal extract is washed with saturated salt solution and the ethereal extract dried ($MgSO_4$). The mixture is concentrated *in vacuo* to yield *L* - N - acetyl - N - nitroso-α - (3,4 - dimethoxybenzyl)alanine.

A mixture of 65.5 g. (1.0 mole) of zinc dust and 100 ml. of water is cooled to 10°. While stirring 75 g. (0.24 mole) of nitroso compound in 150 ml. of glacial acetic acid is added while maintaining the temperature at 10—15°. After addition is finished the mixture is allowed to warm to room temperature over an hour and then warmed to 80° on the steam bath. The mixture is filtered to remove unreacted zinc, and the precipitate washed with three 25 ml. portions of warm 2*N* hydrochloric acid. The combined filtrate is cooled to room temperature and with cooling basified to pH 6.5. The mixture is filtered and the precipitate dried. The residue is extracted with three 200 ml. portions of chloroform. The dried ($MgSO_4$) extract is concentrated *in vacuo* a residue which is recrystallized from methanol to yield *L* - α - N¹ - acetylhydrazino - α - (3,4 - dimethoxybenzyl)propionic acid.

B. Hydrolysis of *L* - α - N¹ - acetylhydrazino - α - (3,4 - dimethoxybenzyl)-propionic acid to *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid

This compound is hydrolysed to *L* - α - (3,4 - dihydroxybenzyl - α - hydrazinopropionic acid as previously described above in Example 1.

EXAMPLE 3

A. Preparation of *L* - α - (*l* - menthoxyacetylhydrazo) - α - (4 - hydroxy - 3 - methoxybenzyl)propionitrile

To a mixture of *DL* - α - hydrazino - α - vanillylpropionitrile (92.3 g., 0.435 moles) in 2 liters of dioxane and 0.5 liter of tetrahydrofuran is added simultaneously *l* - menthoxyacetyl chloride (100 g., 0.430 mole) and triethylamine 58 ml., 0.415 mole). The mixture is agitated at room temperature for 18 hours. The precipitated salts and the solvents are removed leaving an oily mixture. The residue is crystallized from ethyl acetate and hexane to yield 66 g. of product mostly the *Ll* - diastereoisomer.

The crystalline material is recrystallized 3 times from mixtures of ethyl acetate and hexane to yield 12 g. of pure *L* - α - (*l* - menthoxyacetylhydrazo) - α - (4 - hydroxy-3 - methoxybenzyl)propionitrile, m.p. 126—126.5°,

Anal. calcd. for $C_{23}H_{35}N_3O_4$:
C, 66.16; H, 8.45; N, 10.06
Found:
C, 66.21; H, 8.68; N, 10.23

B. Hydrolysis of *L* - α - (*l* - menthoxyacetylhydrazo) - α - (4 - hydroxy - 3 - methoxybenzyl)propionitrile to *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid

Methanol (25 ml.) and conc. hydrochloric acid (30 ml.) is saturated at 0° to —10° with hydrogen chloride gas. To the mixture at 0° is added with stirring the *L* - α - (*l* - menthoxyacetylhydrazo) - α - (4 - hydroxy-3 - methoxybenzyl)propionitrile (3.0 g., 0.0072 mole) and the stirred mixture is allowed to warm to room temperature for 18 hours. The solution is evaporated to dryness and the residue dissolved in a mixture of conc. hydrochloric acid (45 ml.) and acetic

gen per mole starting material. The catalyst is removed by filtration, the filtrate concentrated and the residue recrystallized from methanol-water to yield methyl *L* - α - N^1 - acetylhydrazino - α - 3 - amino - 4 - methoxy benzyl propionate.

To a mixture of the above ester (28.13 g., 0.1 mole) in 300 ml. of dimethoxyethane is added at room temperature 14.81 g. (0.1 mole) of phthalic anhydride in 100 ml. of dimethoxyethane. After addition of 1 g. of 2,4 - dinitrobenzenesulfonic acid the mixture is heated at reflux for 5 hours. The mixture is cooled and concentrated *in vacuo* to dryness. The residue is taken up in ice-cold chloroform and water and the aqueous layer made basic with sodium bicarbonate. The chloroform layer is washed with water, dried over magnesium sulfate and concentrated. The residue is crystallized from methanol-water to yield methyl *L* - α - N^1 - acetyl - N^2 - phthaloylhydrazino - 4 - methoxy - 3 - aminobenzyl propionate.

To 20.57 g. (0.05 mole) of the ester from the previous step in 22 ml. of 50% sulfuric acid at 0—5° is added 3.8 g. (0.055 mole) of sodium nitrite in 15 ml. of water. The stirred mixture is aged in an ice bath for 1 hour, allowed to warm to room temperature and then warmed on a steam bath until the evolution of nitrogen is ended. The mixture is cooled and extracted with ethyl acetate and the extract is dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue is methyl *L* - α - N^1 - acetyl - N^2 - phthaloyl - hydrazino - 4 - methoxy - 3 - hydroxybenzoyl propionate.

B. Hydrolysis of methyl *L* - α - N^1 - acetyl - N^2 - phthaloyl - hydrazino - 4 - methoxy - 3 - hydroxybenzoylpropionate to *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid

The residue is hydrolysed as previously described in Example 1 Step B to yield *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid, m.p. 208° dec.

EXAMPLE 7

A. Preparation of *L* - α - (N^1 - acetyl-N^2 - phthaloylhydrazino) - α - (3,4 - dimethoxybenzyl)propionic acid

To *L* - O - N - diacetyl - α - methylserine (101.6 g., 0.3 mole) in 500 ml. of pyridine is added N - chlorophthalimide (90.79 g., 0.5 mole) and the mixture is boiled for 5 hours. The mixture is concentrated to dryness *in vacuo* taken up in chloroform-water and washed with dilute hydrochloric acid, water and saturated salt solution. The chloroform phase is dried over sodium sulfate, concentrated to dryness *in vacuo* and the residue recrystallized from methanol-water to yield *L* - α - N^1 - acetyl - N^2 - phthaloylhydrazino - α - methyl - β - acetoxypropionic acid.

The acid from the previous step (139.3 g., 0.4 mole) is boiled with 100 ml. of acetic acid and 900 ml. of *N* hydrochloric acid for 3 hours. The mixture is cooled to room temperature, washed and dried at 50° *in vacuo* to yield *L* - α - N^1 - acetyl - N^2 - phthaloylhydrazino - α - methyl - hydracrylic acid.

The acid from the previous step (92.0 g., 0.3 mole) and dicyclohexylcarbodiimide (66.0 g., 0.32 mole) in 500 ml. of benzene are stirred at room temperature for 24 hours. The mixture is filtered, water is added to the filtrate and the benzene phase is successively washed with 5% sodium bicarbonate water and saturated salt solution. The benzene phase is dried over magnesium sulfate and concentrated *in vacuo* and the residue is recrystallized from ethyl acetate - *n* - hexane to yield *L* - α - N^1 - acetyl - N^2 - phthaloylhydrazino - α - methylpropiolactone.

To the lactone from the previous step (57.65 g., 0.2 mole) and veratrole (182.3 g., 1.32 moles) is added all at once 100 g. (0.75 mole) of aluminium chloride. The mixture is heated at 80° for 4 hours, poured over ice and extracted with ether. The ethereal solution is extracted 3 times with cold 1 *N* sodium hydroxide. The aqueous phase is acidified with concentrated hydrochloric acid and extracted with ether and the ether extracted washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue is crystallized from methanol-water to yield *L* - α - (N^1 - acetyl - N^2 - phthaloylhydrazino) - α - (3,4 - dimethoxybenzyl)propionic acid.

B. Hydrolysis of *L* - α - (N^1 - acetyl-N^2 - phthaloylhydrazino) - α - (3,4 - dimethoxybenzyl)propionic acid to *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid

The above acid is hydrolysed as previously described in Example 1 Step B to yield *L* - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid, m.p. 208° dec.

EXAMPLE 8

A solution of methyl L - α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionate (9.6 g., 0.04 mole) in 1 l. of 0.1 M potassium chloride is brought to pH 8.0 by addition of potassiunm hydroxide from a microburette. Approximately 100 units of pig liver esterase is added and allowed to act at 37°. Potassium hydroxide is added as required to maintain the pH at 8.0. After 4 hours the pH is adjusted to 6.4 with hydrochloric acid and the mixture concentrated *in vacuo* to dryness. The residue is extracted with methanol and the recrystallization from water *L*-α - (3,4 - dihydroxybenzyl) - α - hydrazinopropionic acid, m.p. 208° dec. is obtained.